

## **Guidance for Industry**

### **Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Repeat-Dose (90-Day) VICH GL31**

#### **DRAFT GUIDANCE**

**(For Comment Purposes Only)**

The objective of this draft guidance is to establish the minimum recommendations for an internationally harmonized 90-day repeat-dose testing strategy for identifying target organ toxicity and the NOAEL (no-observed adverse effect level) for toxicity of veterinary drug residues in human food based upon repeated dose 90-day toxicity studies for identifying target organ toxicity.

Comments and suggestions regarding the document should be submitted to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>. All comments should be identified with the Docket No. 02D-0368.

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**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Veterinary Medicine  
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# **STUDIES TO EVALUATE THE SAFETY OF RESIDUES OF VETERINARY DRUGS IN HUMAN FOOD/ REPEAT-DOSE (90-DAY)**



Recommended for Consultation  
at Step 4 of the VICH Process  
on 11 April 2002  
by the VICH Steering Committee

THIS GUIDANCE HAS BEEN DEVELOPED BY THE APPROPRIATE VICH EXPERT WORKING GROUP AND IS SUBJECT TO CONSULTATION BY THE PARTIES, IN ACCORDANCE WITH THE VICH PROCESS. AT STEP 7 OF THE PROCESS THE FINAL DRAFT WILL BE RECOMMENDED FOR ADOPTION TO THE REGULATORY BODIES OF THE EUROPEAN UNION, JAPAN AND USA.

# Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food:

## REPEAT-DOSE (90-DAY) TOXICITY TESTING

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***This draft guidance represents the agency's current thinking on establishing the safety of veterinary drug residues in human food and does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative method may be used as long as it satisfies the requirements of applicable statutes and regulations.***

## **1. INTRODUCTION**

### **1.1. Objective of the guidance**

A variety of toxicological evaluations are performed to establish the safety of veterinary drug residues in human food. The objective of this guidance is to establish the minimum recommendations for an internationally harmonized 90-day repeat-dose test testing strategy for identifying target organ toxicity and the no-observed adverse effect level (NOAEL) for toxicity of veterinary drug residues in human food based upon repeated dose 90-day toxicity studies for identifying target organ toxicity.

### **1.2. Background and scope of the guidance**

While rodent and non-rodent toxicity tests have been conducted for decades standardized testing strategies have been delineated by several national and international organizations in the past 20 years. While this guidance recommends the framework for 90-day toxicity testing of veterinary drugs in human food, it is of paramount importance that the design of the test remains flexible. Within the context of this guidance, studies should be tailored to adequately establish the dose-response and a NOAEL for toxicity seen following 90-day compound treatment without introducing redundant or unnecessary test parameters.

### **1.3. General principles**

Adequate toxicity testing involves the administration of repeated doses to assess the effects of repeated exposure to a parent compound and/or metabolites, to define the toxic effects of compounds that accumulate, and to ascertain a dose that does not produce toxicity. As with other types of toxicity testing, available information on the compound should be utilized in designing the test. Repeat-dose toxicity tests should be performed in sensitive/appropriate species. While species selection should always take account of relevance to human metabolism, pharmacokinetics and pharmacodynamics, the generally accepted default species are the rat and the dog. Exposure should begin early enough in life to encompass the growth phase of the test animals. In general, the highest dose should be sufficient to produce toxicity. The data obtained in this test may be used to establish a NOAEL for a veterinary drug.

## **2. GUIDANCE**

### **2.1. Repeat-dose (90-day) toxicity study test**

#### **2.1.1. Purpose**

Repeat-dose (90-day) toxicity testing in one rodent and one non-rodent animal species should be performed (1) to define toxic effects based on repeated and/or cumulative exposures to the

compound and/or its metabolites, (2) to define the nature of the tissue/organ damage, particularly in relation to dose and/or duration of exposure, (3) to identify dosages associated with toxic and biological responses, and (4) to define a NOAEL.

### **2.1.2. Experimental design for a 90-day toxicity test**

Repeat-dose (90-day) toxicity tests should be conducted in accordance with OECD Test Guidelines 408 "Repeated Dose 90-day Oral Toxicity Study in Rodents"<sup>1</sup> and 409 "Repeated Dose 90-day Oral Toxicity Study in Non-rodents."<sup>2</sup>

#### **2.1.2.1. Pathological examination**

Gross necropsy and histopathological examination should be performed in accordance with OECD Test Guidelines 408<sup>1</sup> and 409<sup>2</sup> with the following exception: for non-rodents, histopathological evaluations should be made on a standardized set of tissues plus gross lesions from all animals.

## **3. REFERENCES**

1. OECD. 1998. Test Guideline 408. Repeated Dose 90-day Oral Toxicity Study in Rodents. In: OECD Guidelines for the testing of chemicals. Organisation for Economic Cooperation and Development, Paris.
2. OECD. 1998. Test Guideline 409. Repeated Dose 90-day Oral Toxicity Study in Non-rodents. In: OECD Guidelines for the testing of chemicals. Organisation for Economic Cooperation and Development, Paris.